Modeling the Onset of Cardiac Instability using Probabilistic Cellular Automata

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Abstract

Probabilistic Cellular Automata (PCA) are mathematical models that represent spatially discrete systems as two-dimensional grids of neighboring lattice nodes. We used a PCA with nearest-neighbor interactions to simulate calcium release inside cardiac myocytes to model cardiac instability, a precursor to heart attacks. The states of the nodes are either "on" or "off" according to rules that incorporate randomness. The number of "on" states represents the overall activation of the system, and oscillations in this value indicate instability. The amplitude of these oscillations was studied as a function of the strength of nearest neighbor interactions. For small lattice size, there was a steady, gradual increase in amplitude as interaction strength grew. For large lattice size, the amplitude increase was sudden and sharp. Similar patterns were observed with changes in aspect ratio of the lattice. The results suggest that as the lattice became larger and less oblong, a critical value threshold for onset of oscillations became defined. These simulations helped us understand the dynamics of cardiac myocytes under actual conditions of biological variability and can lead to new hypotheses for future trials.

Background

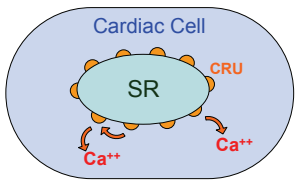
At the start of each heart beat, an increase in intracellular calcium (Ca^{++}) causes cardiac cells to undergo muscular contraction.

Ca^{++} is initially stored in a large central compartment called the Sarcoplasmic Reticulum (SR). The release occurs at discrete locations around the cell through activated "Calcium Release Units". These CRUs exhibit three behaviors:

(1) **Stochastic Activation:** On each beat, a CRU will activate only with a certain probability.

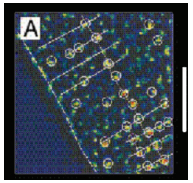
(2) **Interaction:** Once a CRU activates, the released Ca^{++} can trigger neighboring CRUs to also activate

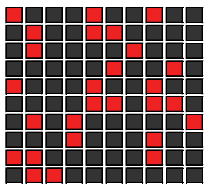
(3) **Refractoriness:** A CRU cannot activate twice in two sequential beats.



Under certain conditions, the total amount of Ca^{++} released becomes unstable from beat to beat, entering a high-low-high-low pattern called "alternans". This periodic instability is a known precursor to cardiac arrhythmia and sudden cardiac death [2].

Design of Probabilistic Automata Model

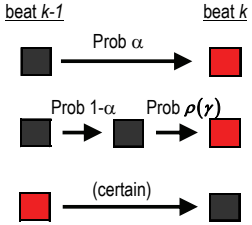




= off
= on (activated)

Left figure [1] shows a mammalian cardiac myocyte and localized calcium release units. Fluorescent dye highlights calcium being released during a heartbeat.

The probabilistic automata model (right) is made up of lattice nodes that demonstrate this phenomenon. Activated lattice nodes are colored red while inactivated stay black. Activation models calcium release in the cell.

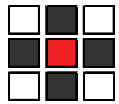


A given lattice node will initially activate from an "off" state on beat $k-1$, to an "on" state on beat k with probability α. A value $r \in [0,1]$ is randomly chosen per lattice node per beat; if $r < \alpha$, then the node activates.

If $r > \alpha$ with probability $1 - \alpha$, then the node is not initially activated. However, it could activate by "nearest-neighbor interactions", with total probability ρ (see below) which depends on the number of activated neighbors during beat k.

If on beat $k-1$ the node was activated, then it is inactivate on beat k.

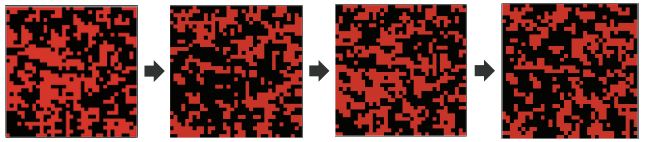
Each node has four nearest neighbors



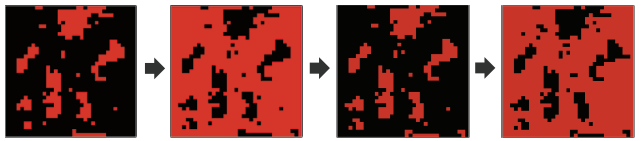
Let σ be the number of activated ("on") neighbors on beat k and γ be the probability of activation via interaction with one neighbor.

Then $\rho(\gamma) = 1 - [1-\gamma]^{\sigma}$ is the total activation probability due to interaction with nearest neighbors.

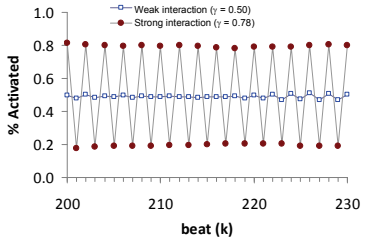
Simulation Results



35 x 35 lattice during four sequential beats with interaction parameter $\gamma = 0.5$ and $\alpha = 0.5$. Each beat has approximately the same amount of activation (no oscillations).



Lattice during four sequential beats with interaction parameter $\gamma = 0.78$ and $\alpha = 0.8$. The activation amount per beat is unstable, and oscillates between high and low values.

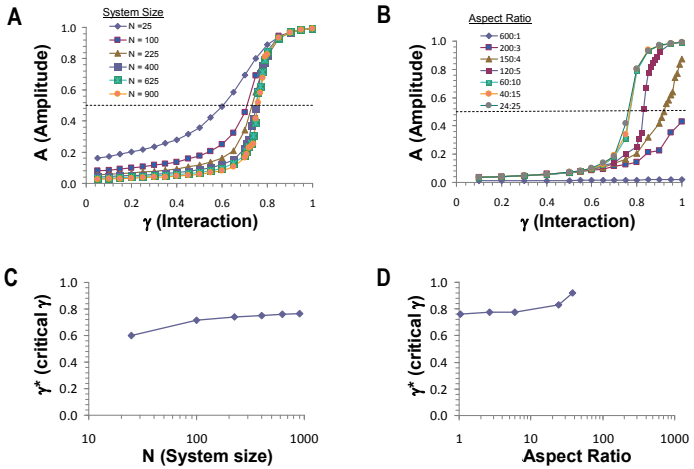


Left: % activation of nodes over time (beats) for weak and strong interaction, showing emergence of oscillation.

Below: Amplitude (A) of oscillation defined as average absolute change in % activated nodes (a_k) over n_k beats.

$$A = \frac{1}{n_k}\sum_{i=0}^{n_k}\left|a_i - a_{i-1}\right|$$

Analysis of Model Behavior



The amplitude (A) of the oscillation increases as interaction (γ) increases (Fig A and B). In Fig A, as system size increases from N = 25 (5 x 5) to N = 900 (30 x 30), the transition to large oscillations becomes more sudden. The value of γ at which 50% amplitude is achieved is the critical γ (γ^*) and defines the transition point. A similar definition is made for Fig B, in which aspect ratio (the ratio of the length to the width) of an $N = 600$ lattice increases from near 1.0 (for 24 x 25) to 600 (for 600 x 1), and the transition is sharper for smaller aspect ratios.

In Fig C, γ^* initially increases but then levels off as the system size gets larger. In Fig D, γ^* starts to increase rapidly as the aspect ratio surpasses 120:5 and the lattice shape becomes increasingly oblong. Past 150:4, γ^* does not exist, indicating the system cannot achieve oscillation at these aspect ratios.

CONCLUSIONS: The emergence of unstable behavior in the form of oscillations is sensitive to both size and shape of the lattice. A large system size coupled with increased aspect ratio discourages the presence of oscillation. This is in line with the observed size and shape of real myocytes, in which oscillations are detrimental and may lead to arrhythmias.

References

[1] Cleemann L, Wang W, and Morad M. Two-dimensional confocal images of organization, density, and gating of focal Ca^{2+} release sites in rat cardiac myocytes. Proc Natl Acad Sci USA 95, 18 (Sep 1998), 10984–10989.

[2] Clusin WT. Mechanisms of calcium transient and action potential alternans in cardiac cells and tissues. Am J Physiol Heart Circ Physiol 294:H1-H10 (2008).